#12/13 BP 8-14 (NE)

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Mar Tormo
Ana M. Tari
Gabriel Lopez-Berestein
Timothy J. McDonnell

Serial No.: 09/381,747

Filed: September 22, 1999

For: INHIBITION OF BCL-2 PROTEIN EXPRESSION BY LIPOSOMAL ANTISENSE OLIGODEOXYNUCLEOTIDES

Group Art Unit: 1635

Examiner: K. Lacourciere

Atty. Dkt. No.: UTSC:550/DLP

I. AMENDMENT; II. RESPONSE TO OFFICE ACTION DATED FEBRUARY 1, 2001, AND III. REQUEST FOR EXTENSION OF TIME

Commissioner for Patents
Washington, D.C. 20231

Commissioner:

This paper is submitted in response to the Office Action dated February 1, 2001 for which the three-month date for response was May 1, 2001.

A request for a three-month extension of time to respond is included herewith along with the required fee. This three-month extension will bring the due date to August 1, 2001, which is within the six-month statutory period. Should such request or fee be deficient or absent, consider

this paragraph such a request and authorization to withdraw the appropriate fee under 37 C.F.R. §§ 1.16 to 1.21 from Fulbright & Jaworski L.L.P. Account No.: 50-1212/10017145/DP01982.

Reconsideration of the application is respectfully requested.

I. AMENDMENT

Please make the following amendments:

In the Claims

Please cancel claims 21 and 50-60.

Please amend claims 24 and 25 to read as follows:

24. The composition of claim 23, wherein said liposome consists essentially of neutral lipids.

25. The method of claim 10, wherein said antisense polynucleotide is a P-ethoxy polynucleotide.

II. RESPONSE TO OFFICE ACTION

A. Status of the Claims

Claims 1-60 were pending at the time of the present Action. Claims 50-60 were withdrawn in the instant Action, and are canceled herein, as being drawn to a non-elected invention. Applicants reserve the right to pursue the subject matter of claims 50-60 in a later filed divisional application. Claim 21, 24 and 25 were amended to correct minor typographical errors.

B. The Oath/Declaration is Corrected

The Action next notes that the oath or declaration continues to be defective. The Examiner states that the new declaration submitted with Applicants' previous Response is defective in that it contains only the name of inventor Tormo. A new declaration in compliance

with 37 CFR 1.67(a) is submitted herewith. Applicants respectfully request that this rejection be withdrawn.

C. Double Patenting is Avoided

1. Rejection based on co-pending application No. 08/726,211

The Examiner states that Claims 10-20 and 39-49 conflict with claims 10-30, 44, and 46 of co-pending application No. 08/726,211, and are provisionally rejected under the judicially created doctrine of double patenting. Applicants will address the issue of double patenting for claims 10-20 and 39-49 when the provisional double patenting rejection becomes a double patenting rejection upon the issuance of either the current application or application No. 08/726,211 by filing a terminal disclaimer.

2. Rejection based on U.S. Patent No. 5,855,911 in view of Evan or Green or Reed in further view of Tormo

The Action next rejects claims 1-9 and 21-38 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 5,855,911 in view of Evan or Green *et al.* or Reed *et al.* in further view of Tormo *et al.* The '911 patent is said to generally claim compositions which comprise an antisense oligonucleotide, including a p-ethoxy oligonucleotide, and a neutral lipid. The Action acknowledges that the '911 patent does not teach compositions where the antisense oligonucleotide is targeted to bcl-2 or where the antisense oligonucleotide comprises SEQ ID NO:1. Evan and Reed are said to teach the use of an antisense oligonucleotide targeted to bcl-2 to prevent or inhibit the expression of the Bcl-2 protein. Tormo is said to teach a p-ethoxy antisense oligonucleotide targeted to bcl-2, delivered using a liposome composition. Applicants respectfully traverse.

Applicants initially point out that the Tormo abstract is not available as prior art in that it bears a publication date less than one year prior to the priority date of the present application and

was published on behalf of the present inventors, and thus is not available under 35 USC 102(a) or (b). Applicants have enclosed an appropriate Disclaiming Declaration to demonstrate that the other named authors of the Tormo *et al.* article, M. Khodadadlan, M. Cabanillas and F- Garcia-Conde, did not contribute conceptually to the subject matter of the claimed invention.

Moreover, the relevance of Tormo *et al.* is limited, at best, in that Tormo fails to disclose that the liposomes are "neutral" liposomes as specified by the claims. Thus, Tormo fails to provide the necessary link between references relied upon to teach the bcl-2 antisense (Evan, Reed and Green) and that relied upon to teach neutral liposomes (the '911 patent). As such, there is no basis for correlating the teachings of Evan, Reed or Green with that of the '911 patent claims to reach a conclusion of obviousness-type double patenting.

In light of the fact that the Tormo et al. reference fails to teach or suggest the concept of neutral liposomes, and the fact that it is not available as prior art, it is respectfully submitted that the obviousness-type double patenting rejection is inappropriate.

3. Rejection based on U.S. Patent No. 6,042,846 in view of Evan or Green or Reed in further view of Tormo

The Action next rejects claims 1-9 and 21-38 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-6 of U.S. Patent No. 6,042,846 in view of Evan or Green *et al.* or Reed *et al.* in further view of Tormo *et al.* The '846 patent is said to generally claim compositions which comprise an antisense oligonucleotide, including a p-ethoxy oligonucleotide, and a neutral lipid. The Action acknowledges that the '846 patent does not teach compositions where the antisense oligonucleotide is targeted to bcl-2 or where the antisense oligonucleotide comprises SEQ ID NO:1. Evan and Reed are said to teach the use of an antisense oligonucleotide targeted to bcl-2 to prevent or inhibit the expression of

the Bcl-2 protein. Tormo is said to teach a p-ethoxy antisense oligonucleotide targeted to bcl-2, delivered using a liposome composition. Applicants respectfully traverse.

Applicants respectfully incorporate by reference the argument set forth above with respect to the double patenting rejection over the '911 claims, as the issues are the same.

D. The Claims Are Definite

Next the Action asserts that independent claims 21, 24, 25 and 36 and dependent claims are indefinite for failing to particularly point out and distinctly claim the subject matter of the invention. The rejections of claims 21, 24 and 25 are all based on an alleged lack of antecedent basis for certain phrases in the claims. The rejection of claim 36 based on the recitation of "a second, bcl-2 encoding polynucleotide" without reciting a first bcl-2 encoding polynucleotide. Applicants respectfully traverse.

Claim 21 has been canceled and claims 24 and 25 have been amended herein to correct inadvertent typographical errors. For example, claim 21 recited "at least 8 nucleotides" which subject matter is now reflected in claim 36. As such, claim 21 is redundant and has been canceled for this reason. With respect to claim 24, the word "association" in claim 24 was inadvertently left in the claim during the drafting/revising stage and the word "composition" in claim 25 should have been "method." These amendments are made simply to correct inadvertent mistakes in the claims and are not meant to limit the original scope of the claims in any way.

Claim 36 is not amended because it is believed to be clear in its current form. Applicants point out that there is a "comma" after the term "second" in claim 36, as is also shown on page 6 of the Official Action. Following commonly accepted grammar, the comma indicates to the skilled artisan that the terms "second" and "Bcl-2-encoding" are each separate modifiers of the term "polynucleotide." That is, the term "second" is meant only to modify the term "polynucleotide" and does not modify the term "Bcl-2-encoding." Thus, claim 36 essentially

recites "A composition comprising a first . . . polynucleotide that hybridizes to a second . . . polynucleotide . . .", wherein the first polynucleotide is further defined as an antisense polynucleotide and the second polynucleotide is further defined as a Bcl-2-encoding polynucleotide.

For the foregoing reasons, Applicants respectfully request that the definiteness rejections be withdrawn.

E. <u>The Claims Are Enabled</u>

Claims 10-20 and 39-49 are rejected under 35 U.S.C. 112 first paragraph as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains to make and use the invention.

The Action now acknowledges that the specification as filed provides examples of *in vitro* treatment of cells using compositions which comprise a neutral liposome and bcl-2 targeted antisense. The Action further acknowledges that the specification provides an example wherein nude mice injected with follicular lymphoma cells were treated with a liposomal composition comprising antisense targeted to bcl-2 and that some mice exhibited a reduction in proliferation of the injected lymphoma cells. Nevertheless, the Action continues to assert that no evidence is provided that the claimed protocol would be effective in humans for the treatment of any bcl-2 associated disease given the inherent unpredictability of antisense technology.

With respect to the enablement requirement, it is well settled patent law that the first paragraph of § 112 requires nothing more than objective enablement. *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). This objective enablement may be provided through broad terminology or illustrative examples. *Id.* The PTO bears the initial burden, in rejecting a claim under the enablement requirement of § 112, to set forth "a reasonable explanation as to why it believes that the scope of protection provided by that claim is not

adequately enabled by the description of the invention provided in the specification of the application." *Wright*, 999 F.2d at 1561-62 (citing *Marzocchi*, 439 F.2d at 223-24, 169 USPQ at 369-70).

The MANUAL OF PATENT EXAMINING PROCEDURE (MPEP) explains that, in setting forth an enablement rejection, an examiner must provide reasons for the uncertainty of the enablement after considering the invention as a whole. MPEP § 2164.04, page 2100-150 (July 1998). In response, the Applicant must present persuasive arguments, supported by suitable proofs where necessary, that one skilled in the art would be able to make and use the claimed invention using the application as a guide. *Id* (citing *In re Brandstadter*, 484 F.2d 1395, 1406-07, 179 U.S.P.Q. 286, 294 (C.C.P.A. 1973)). Applicants submit that the Examiner has not considered the invention as a whole in setting forth the present enablement rejection. As stated above, the invention as a whole is drawn to the a method of inhibiting a Bcl-2-associated disease comprising obtaining an antisense polynucleotide that hybridizes to a Bcl-2-encoding polynucleotide under intracellular conditions, mixing the antisense polynucleotide with a neutral lipid to form a polynucleotide/lipid association, and administering said association to a cell, wherein said cell expresses both Bcl-2 and Bax, thereby inhibiting growth of said cell.

Applicants presented a plethora of evidence in the Response to Office Action filed on November 10, 2000, showing that the methods of the invention are enabled. In response to Applicants' arguments, the current Action simply states that the arguments are not persuasive. Although Applicants submitted affidavits and publications supporting their position, the Action contends that "there is no evidence that the mouse model disclosed would reasonably correlate with the therapeutic results claimed." Despite the provision of "numerous examples wherein a mouse model may correlate with a therapeutic outcome in humans," the Action maintains that

the examples are not applicable because they are used to test small molecules and not to demonstrate the therapeutic effect for antisense molecules. However, the Action provides no evidence negating Applicants' affidavits supporting the enablement of the invention.

It is submitted that the Action has essentially set forth a rejection based on the "utility" requirement inherent in § 112, first paragraph. The Federal Circuit and its predecessor court have addressed satisfaction of the utility requirement in the context of pharmacological or therapeutic inventions in a number of cases. For example, in *Nelson v. Bowler*, 626 F.2d 853, 206 U.S.P.Q. 881 (C.C.P.A. 1980), the court found that the mere identification of a pharmacological activity of a compound that is relevant to an asserted pharmacological use satisfies the utility requirement. *Nelson*, 626 F.2d at 856, 206 U.S.P.Q. at 883. Similarly, in *Cross v. Iizuka*, 753 F.2d 1040, 224 U.S.P.Q. 739 (Fed. Cir. 1985), an interference, the court affirmed a finding that a pharmacological utility had been disclosed.

The invention in *Cross* related to a chemical compound used for treating blood disorders. Cross had challenged the evidence in Iizuka's specification that supported the claimed utility. Commenting on the significance of data from *in vitro* testing, the *Cross* court explained:

> We perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, *in vitro* testing, may establish a practical utility for the compound in question. Successful *in vitro* testing will marshal resources and direct the expenditure of effort to further *in vivo* testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an *in vitro* utility.

Cross, 753 F.2d at 1051, 224 U.S.P.Q. at 747-48.

The recent Federal Circuit case of *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995) is also relevant. In *Brana*, the Federal Circuit considered a "utility" rejection, set forth under § 112, first paragraph, of claims drawn to 5-nitrobenzo[de]isoquinoline-1,3-dione compounds, for use as anti-tumor substances. *Brana*, 51 F.3d at 1562. The specification in *Brana* described the

claimed compounds as providing "a better action and a better action spectrum as antitumor substances" than known benzo[de]isoquinolines and specifically compared the claimed compounds to those compounds analyzed in K.D. Paull *et al.*., *Computer Assisted Structure-Activity Correlations*, DRUG RESEARCH, 34(II), 1243-46 (1984). In his final rejection of the claims under § 112, first paragraph, the Examiner asserted that the specification lacked any teaching of any specific disease against which the claimed compounds were active. The Examiner further maintained that the tests disclosed in the specification and in Paull were not sufficient to establish a reasonable expectation that the claimed compounds had a practical utility.

In addressing the Examiner's rejection, and the Board's affirmation of the rejection, the *Brana* court noted that, contrary to the Commissioner's position, the tumor models tested in Paull adequately represented a specific disease against which the claimed compounds were allegedly effective. The court also reiterated the standard for finding that a specification satisfies the "how to use" requirement of § 112, first paragraph, stating:

> [A] specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented *must* be taken as in compliance with the enabling requirement of the first paragraph of § 112 *unless* there is reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support.

Brana, 51 F.3d at 1566 (quoting *In re Marzocchi*, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971). (underlined emphasis added).

In *Brana*, the Commissioner argued that *in vivo* tests in animals, such as those illustrated in Paull, were merely preclinical tests used simply to ascertain whether the compounds tested are suitable for the second stage of testing, apparently referring to *in vivo* testing in humans. Therefore, the Commissioner asserted, the tests did not sufficiently predict the success of the claimed

compounds for treating cancer in humans. *Id.* at 1567. However, as the *Brana* court pointed out, the requirements for obtaining a patent are not the same as the requirements for obtaining government approval to market a particular drug for human consumption. *Id.* In fact, the court explained that "the stage at which an invention . . . becomes useful is well before it is ready to be administered to humans." *Id.* at 1568. Applicants have presented ample evidence to support the usefulness of the claimed invention.

The affidavits and other evidence previously submitted by Applicants more than sufficiently support the enablement and utility of the claimed invention. Thus, in light of the foregoing, it is respectfully requested that the enablement rejection be withdrawn.

F. The Claims Are Patentable Over Evan or Reed or Green each in view of Tari and Tormo

The Action next asserts that claims 1-9 and 21-38 are obvious over Evan or Reed or Green, each in view of Tari and Tormo. Evan is said to teach the use of an antisense molecule target to Bcl-2 to prevent the expression of the Bcl-2 protein, targeting the oligonucleotide comprising SEQ ID NO:1 to the translation initiation codon of bcl-2. Reed is said to teach an antisense oligonucleotide which is targeted to bcl-2 and inhibits the expression of the bcl-2 protein. Reed is also said to teach delivery via a liposome. Green is said to teach antisense oligonucleotides targeted to anti-apoptotic genes, including bcl-2. Green is further said to teach that the oligonucleotides can be encapsulated into liposomes for administration.

The Action acknowledges that neither Evan or Reed or Green teaches a liposome composed of neutral lipids, antisense with a p-ethoxy backbone modification, or liposomes composed of phosphatidylcholine, phosphatidylglycerol, phosphatidylethanolamine, or dioleoylphosphatidylcholine. Tari is said to teach antisense oligonucleotides encapsulated in a liposome comprised of neutral lipids, including liposomes composed of phosphatidylcholine,

phosphatidylglycerol, phosphatidylethanolamine, or dioleoylphosphatidylcholine. Tormo is said to teach an antisense oligonucleotide targeted to bcl-2 with a p-ethoxy backbone modification.

The Action takes the position that it would have been obvious to the skilled artisan to combine the teachings of the cited references to make a composition of an antisense oligonucleotide targeted to the translation initiation codon of bcl-2 encapsulated in a lipid with a p-ethoxy backbone using the formulations taught by Tari. The alleged motivation for combining the cited references is said to be "for the benefit of nuclease resistance." Applicants respectfully traverse.

The presently claimed invention is directed to uncharged liposome compositions comprising Bcl-2 related antisense P-ethoxy constructs, and methods of use therefor. Applicants initially note that this appears to be a new rejection in that Tormo has not previously been applied. The previous Action set forth a rejection based upon Evan or Reed or Green in view of Tari. That rejection has presumably been overcome in light of the statement at page 16 of the current Action that "any rejection of record not repeated in this Action is withdrawn." Tormo was published in 1996, less than one year prior to the filing of the present application, and is removed from availability as prior art by virtue of the disclaiming declaration included herewith. The current rejection appears to hinge on Tormo's teaching of the p-ethoxy backbone. Without Tormo's teachings, one does not arrive at the presently claimed invention by combining the teachings of Evan, Reed or Green with Tari. Moreover, the relevance of Tormo *et al.* is limited, at best, in that Tormo fails to disclose that the liposomes are "neutral" liposomes as specified by the claims. Thus, Tormo fails to provide the necessary link between references relied upon to teach the bcl-2 antisense (Evan, Reed and Green) and that relied upon to teach neutral liposomes.

As such, there is no basis for correlating the teachings of Evan, Reed or Green with that of Tari. For the foregoing reasons, it is submitted that the rejection is overcome.

Nevertheless, the Action sets forth arguments rebutting Applicants' previous arguments regarding Tari. Therefore, those statements will be addressed herein for the sake of completeness. For example, the Action asserts that Tari does expressly teach that neutral lipids are preferred over a charged lipid. This assertion is based on Tari's statement that the preferred lipids are selected from phosphatidylcholines and phosphatidylserines, with DOPC (a neutral lipid) being particularly preferred. The Action misses the point of Applicants' arguments.

As Applicants pointed out in the Response to Office Action filed on November 10, 2000, Tari provides a ***general*** discussion of lipids. While both charged and uncharged lipids are discussed therein, Tari provides absolutely no motivation or suggestion for preferably combining neutral lipids with P-ethoxy polynucleotides that hybridize to a Bcl-2-encoding polynucleotide to form a neutrally-charged polynucleotide/lipid association. Of course, that is what is required in order for the combined cited references to obviate the claimed invention.

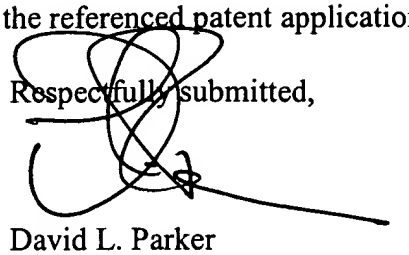
In light of the foregoing, it is respectfully requested that the obviousness rejection be withdrawn.

G. Conclusion

This is submitted to be a complete response to the referenced Official Action. Applicants submit that, in light of the foregoing remarks, the present case is in condition for allowance and such action is respectfully requested.

The Examiner is invited to contact the undersigned attorney at (512) 536-3055 with any questions, comments or suggestions relating to the referenced patent application.

Respectfully submitted,



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